

**REMARKS**

Upon entry of the amendments herein, claims 22-26, 28-33 and 35-40 remain pending in the application. Claims 22, 26, 29, 30, 33, 34, 36 and 38 have been amended; and claim 34 has been cancelled. No new matter has been introduced by any of the amendments herein.

The Examiner has maintained the various indefiniteness rejections set forth in the previous Office Action. In the first place, the Examiner asserts that the "normalizing" step of claims 22 and 33 is unclear, since "no amino acids are involved in the preceding step...." These claims have been amended herein by addition of "assigning" and "evaluating" steps to clarify that the instantly claimed method includes the assignment of spheres of fixed radius or other space-filling generic side chains to each position in a generated configuration where an amino acid residue would be. Thus, any gaps perceived by the Examiner in recitation of the method steps have been filled. Support for these claim amendments can be found in the specification on, for example, page 8.

Thus, it is clear from the amended claims how "normalizing" as defined in the application can be carried out and clear "what is a 'total surface' as related to the backbone." The disclosure on pages 8 and 9 adequately describes how the spheres

are assigned and positioned (the "assigning step"), how surface exposure is determined (the "evaluating" step) and how the "normalizing" step follows out of those steps.

Claim 22 has also been rejected for the alleged indefiniteness of the terms "random set of sequences," "uniform weight" and "allowed sequences." All of these terms have been deleted from the "generating" step of the claim by amendment herein, and new language, reflecting the amendments to claims 22 and 33 discussed above, has been inserted. The amended step clearly recites how said step is to be carried out. Furthermore, the newly added "assigning" and "evaluating" steps render moot the Examiner's concern about the meaning of hydrophobicities in the context of a backbone configuration.

Furthermore, as explained on page 9, lines 23-31 of the specification, the hydrophobicities of the natural amino acids have been experimentally measured and, furthermore, one can easily use these measured hydrophobicities or simplify the process to assign hydrophobicity values from the set of real numbers from 0 to 1, inclusive. Thus, a sequence of hydrophobicities merely refers to the string of values assigned the various residues in a given sequence.

Claim 22 also remains rejected as indefinite because of the alleged lack of clarity in the "determining" and "recording"

steps. The Examiner states: "beginning of the description of the method step suggests that one configuration corresponds to one sequence, but following part of the phrase suggest [sic] that many sequences can fall within one configuration."

Applicants maintain that there is no conflict between the use of the word "configuration" (singular) in some instances and the word "configurations" (plural) in others. Nonetheless, both the "determining" and "recording" steps have been simplified by amendment herein and the issue no longer exists.

Claim 22 has further been rejected as indefinite for its recitation of a "synthesizing" step for two reasons. With respect to the first issue, that raised earlier concerning failure to recite any specific amino acids, Applicants refer again to the introduction of the "assigning" and "evaluating" steps into the claim. With respect to the second issue, Applicants have amended the claim to change the step in question from one of "synthesizing" to one of "selecting," more in keeping with a "method-for-designing" claim.

Claims 28 and 35 have been rejected as being unclear as to what a non-compact configuration is. In their previous response, Applicants directed the Examiner's attention to the disclosure in the last paragraph of page 8 of the specification. Once again, the Examiner viewed this as unpersuasive because of

the distinction between backbone configurations and actual sequences wherein the amino acids at each position are defined. Again, this rejection is rendered moot in light of the introduction of the "assigning" and "evaluating" steps into claim 22..

With respect to the employment of the method of Flower in the calculation of total surface area, the Examiner implies that the method is inadequate because it is a calculation of compactness and not total surface area that is wanted. However, anyone of skill in the art would readily recognize that total surface area and compactness are closely related; the greater the total surface area, the less compact the configuration is. Thus, the method of Flower is perfectly appropriate for the determination of a desirable degree of compactness based on the preset threshold level.

Claims 29, 36 and 38 have been rejected on the grounds that several terms are indefinite. In their previous response, Applicants directed the Examiner's attention to the passage in the specification running from page 10, line 27 through page 11, line 5. The Examiner has dismissed this disclosure, inappropriately, as not presenting clear answers to the issues raised.

The first term cited by the Examiner is "sufficiently similar." As clearly explained in the paragraph running from the bottom of page 10 through the top of page 11, one configuration is considered to be "sufficiently similar" to another if it can be placed in the same cluster of configurations. The procedure for determining clustering, which involves determination of total root-mean-square distances and using a defined root-mean-square distance  $\lambda$ , is also set forth in this passage.

It is further not clear to the Examiner "how 'clustering configurations' is 'followed by their backbones.'" It should be clear from the description of the invention and the claim language that what are sufficiently similar are the trajectories of their (the configurations') backbones. Nonetheless, in the interest of expediting prosecution of the application and providing greater clarity, Applicants have amended claims 29, 36 and 38 so that there can be no doubt as to the connection between "trajectory" and "backbone."

The Examiner has further found indefinite the phrase "treating all configurations within a cluster as variants of a single configuration." It is not clear to Applicants precisely what the Examiner's objection is. The Examiner is again referred to the paragraph running from the bottom of page 10 to

the top of page 11. The cited disclosure, combined with that found on page 10, lines 21-26, fully explains the relationship among the concepts of "similarity," "clustering" and "variant" in the context of the present invention and provides sufficient guidance as to the meanings of these related terms. Thus, the rejected claims are in conformance with the requirements of 35 USC §112, second paragraph. Nonetheless, the phrase in question in claims 29, 36 and 38 has been amended in an attempt to remedy the Examiner's confusion.

The Examiner further asserts with respect to claims 29, 36 and 38 that "the term 'designability of the cluster' and its involvement in the method step, is not clear." In the first place, Applicants wish to point out that the phrase is clearly defined in the specification on, for example, page 11, lines 6-8. Furthermore, the "summing" step of these claims has been amended by deletion of the phrase in question. Still further, a new "identifying" step, again fully supported by the specification, has been added to make clearer the relationship of the concept of designability to the "summing" step and indeed the entire design process.

Claims 30 and 34 have also been rejected as indefinite. The Examiner asserts that it is not clear in these claims which configurations the phrase "each configuration" refers to. Claim

30 has been amended to put it in independent form. Amended claim 30 contains the "Variance" steps of the original claim plus all of the steps of claim 22 except those involving "sequences of hydrophobicities." Thus, amended claim 30 clearly recites an alternate design method which employs the concept of Variance rather than use of hydrophobicities. This claim is fully supported, and Variance fully defined, on page 13 of the instant specification. In any event, the amendment of claim 30 herein renders moot the Examiner's concern about what the phrase "each configuration" refers to. Furthermore, the amended claim addresses the Examiner's concern that the claim language conveyed that the design process only begins with the last step.

Claim 34 has been cancelled in the wake of the amendment of claim 30, and its rejection is thus rendered moot.

The claims remain rejected under 35 USC §112, first paragraph as not being enabled by the disclosure. The Examiner maintains that selection of amino acids is critical to the practice of the invention but not included in the claims and not enabled by the disclosure. Again, Applicants refer to the "assigning" and "evaluating" steps introduced into claim 22 by amendment herein.

Contrary to the Examiner's assertion, it is not necessary to select specific amino acids in the early steps of the design

process. By assignment of generic spheres or other space-filling shapes to the positions that amino acid residues would occupy in a generated configuration, one of ordinary skill in the art would, in fact, easily be able to implement the subsequent method steps referred to by the Examiner such as, for example, eliminating self-intersecting configurations and evaluating surface exposures.

In tandem with the rejection just discussed, the Examiner has rejected the claims under 35 USC §101/§112, first paragraph, maintaining that "the claimed invention is not supported by either a credible utility or a well established utility" [emphasis added] and that one skilled in the art would not know how to use the claimed invention. It must be reemphasized that such assertions could only possibly be appropriate if the claimed invention were the proteins themselves designed by the instantly claimed method or if the claimed invention were methods of using said proteins; neither is the case. The claimed invention is a method for designing proteins. Most critically, the Examiner has not met the fundamental requirement of establishing a *prima facie* case of no utility.

The utility of the claimed invention is as a means of applying the powerful computational tools available today to test myriad combinations of backbone configurations and amino



acid sequences and to thereby determine novel structures that have potential "real world" application. In this case the design tool itself is the "real world" application. In the first place, the instantly claimed invention provides a means for eliminating myriad combinations that, upon application of the algorithm, can clearly be seen to be of no use. Thus, merely by greatly reducing the number of possibilities from which to choose, the instantly claimed invention has a "real world" utility and constitutes an improvement in the state of the art.

The Examiner has stated that his basis for this rejection comes from the "'how to use' prong of the enablement requirement." Contrary to the Examiner's assessment, the "how to use" of the invention is not the utilities or properties of proteins that may be designed by the claimed method. Rather, the "how to use" of the invention lies in the steps set forth in the claims, steps that enable the designing of new proteins. How to carry out this use is clearly set forth in the specification and claims. As described in the specification, by employment of the claimed methods one can design new protein structures with novel protein folds, which folds have a high likelihood of having the properties normally attributed to real proteins,

namely mutational stability, thermodynamic stability and rapidity of folding.

The Examiner has also stated that he has not found "an adequate nexus between the evidence of record and the asserted properties of the claimed subject matter." Applicants ask: what properties are asserted for the claimed subject matter? Polypeptides are not being claimed, so whether or not possible uses of the designed polypeptides are disclosed in the instant specification and whether or not this disclosure is an invitation to experiment are irrelevant. The properties asserted for the claimed subject matter are speedy and efficient determination of the designability of protein structures and, hence, potential suitability of said structures for "real world" applications.

The Examiner continues to cite the teaching of Shakhnovitch as providing grounds for the assertion of nonutility of the instant invention. By the Examiner's reasoning, no potential inventors should ever bother to try to come up with an algorithm or other tool for designing proteins, since previous efforts along these lines "have largely been unsuccessful." The mere citing of an opinion given in a reference does not constitute the "form of support used in establishing the factual basis of a

*prima facie* showing of no utility...." MPEP 706.03(a)(1),  
Guideline (C)(2).

The question really should be whether or not one of skill in the art would find credible the assertion that the presently claimed method represents a potential improvement in the area of protein design and whether or not one of skill would have a reasonable expectation that the instantly claimed method could lead to the design of new, useful proteins. Applicants have met these criteria for establishing utility, and the rejection should be withdrawn.

It cannot be emphasized enough that the Examiner has confused the utility standards with respect to compositions of matter and the utility standards for the presently claimed subject matter. The Examiner asserts that "identifying use of the claimed polypeptide would require carrying out further research." It must be noted in the first place that there is no "claimed polypeptide" in this application. This fact alone points out the untenability of the rejection.

Applicants do not argue with the idea that further study would be required to determine the uses of any polypeptides that might be designed by the claimed method. However, and regardless of how much research might actually be required, the fact is that such use and the research required to determine it

would be the subject of an entirely separate patent application. The Examiner's contention that Applicants' disclosure of potential utilities is an invitation to do further research is without relevance to the analysis of patentability of the claimed invention. Not only have no polypeptides been claimed, but, as the Examiner should take note, no method-of-treatment claims have ever been presented for examination in the instant application.

One can employ the methods of the instant application to design proteins with a high potential for utilities of the kind attributed to naturally occurring proteins. Subsequent determination of which of these potentially useful proteins actually have therapeutic and/or other uses, and determination of precisely what these uses might be, is not the subject of the present application, and it is inappropriate to reject the application for lack of such disclosure. "An invention has a well-established utility if a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties of a product or obvious application of a process)." [Emphasis added.] MPEP 706.03(a)(1). Applicants have both made a strong case for the "obvious application" of their invention and have provided sufficient guidance on how to carry out said invention.

Applicants wish further to point out that there are a number of examples of issued patents that recite algorithms to be used in the design of proteins. As just one example of such a patent, Applicants direct the Examiner's attention to US 6,205,404 to Michaels, et al., a copy of which is provided herewith as part of an Information Disclosure Statement. This patent is typical of others in the field in not providing any particular examples of the proteins that can be designed by employing the algorithm which is at the heart of the invention. There is nothing about the present application or the context in which it should be examined that makes the instantly claimed subject matter any more deficient in meeting the accepted criteria for establishing patentable utility than the subject matter claimed in issued patents in the same area.

Finally, Applicants recall that, in Paper No. 10, the Examiner leveled a rejection of the claims under 35 USC §103(a) as obvious over US 5,612,895 to Balaji, et al. in view of US 5,878,373 to Cohen, et al. or US 5,241,470 to Lee, et al. In their response to the rejection, Applicants set forth in clear, cogent terms the reasons why the cited combinations of references are ineffective as bars to patentability.

The Examiner's response in Paper No. 12 (a final rejection) to these arguments was merely to state that the rejection was

maintained; no comment whatsoever was made on the arguments presented. This is clearly in violation of 37 C.F.R. §1.113(b), wherein it is stated: "In making such final rejection, the examiner shall repeat or state all grounds of rejection then considered applicable to the claims in the application, clearly stating the reasons in support thereof." Reference is also made to MPEP §706.07, wherein it is stated in connection with making a final rejection that "where a single previous Office action contains a complete statement of a ground of rejection, the final rejection may refer to such a statement and also should include a rebuttal of any arguments raised in the applicant's reply."

In response to the final rejection, Applicants filed (on March 31, 2003) an RCE which was accompanied by another bona fide response to, inter alia, the outstanding prior art rejection. The response included all of the previously submitted arguments as well as additional arguments in support of the inappropriateness of the cited prior art. This time, the Examiner's response was to arbitrarily deem it "necessary to resolve issues addressed in rejections under 35 U.S.C. 112, first and second paragraphs prior to applying appropriate art rejections."

This action is clearly not in accord with MPEP §707.07(g) wherein it is stated that piecemeal examination should be avoided as much as possible and that the examiner should reject each claim on all valid grounds available. Applicants further note that none of the situations enumerated in §707.07(g) as being ones where limiting action to less than all the outstanding issues is appropriate apply to the current application.

The end result is that Applicants have made two bona fide responses to the prior art rejection and have not received a single comment from the Examiner on the merits of, or the alleged flaws in, said arguments. Applicants have made a good faith effort herein to amend the claims to address all of the Examiner's expressed §112 concerns and to put the claims in best condition for allowance. Furthermore, they have clearly pointed out how the instantly claimed invention is patentable over the cited prior art.

However, should the Examiner continue to maintain that the application is not allowable, it is Applicants' intention to appeal. Thus, in addition to the reasons set forth above, the Examiner is obliged to respond substantively to Applicants' arguments against the obviousness rejection in order that, should the case go up on appeal, the record is clear as to all

of the issues that remain outstanding. A copy of Applicants' March 31, 2003 Response, containing all of the arguments of record against the prior art rejection, is provided herewith for the Examiner's convenience. The arguments are found on pages 4-6 of the document.

In view of the arguments set forth above and the amendments made herein by way of more particularly describing the subject matter regarded as the invention, all of the outstanding §§101 and 112 rejections have been responded to and overcome. Furthermore, Applicants' earlier arguments against the obviousness rejection, never commented on by the Examiner, show the patentable distinctness of the claimed invention over the cited prior art. Accordingly, the application is in condition for allowance; reconsideration and allowance of the application with pending claims 22-26, 28-33 and 35-40 are respectfully requested. Should any other matters require attention prior to allowance, it is requested that the Examiner contact the undersigned.



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The Commissioner is hereby authorized to charge any fees  
which may be due in connection with this communication to  
Deposit Account No. 23-1703.

Dated: August 9, 2004

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Richard J. Sterner", written over a horizontal line.

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Enclosure